

 Trifluoroacetic acid (1ml) was added to a suspension of (SEQ ID NO: 2) BHAlyslys₂lys₄lys₈DBL₁₆ (36.5mg; 5.0μmol) in dry dichloromethane (1ml) and the resulting solution stirred at room temperature under nitrogen for two hours and then concentrated. The residue was dissolved in dry DMSO (2ml) and the pH adjusted to 8.5 with triethylamine. A solution of the crude tetrabutylammonium 4-nitrophenyl N-(2-sulfoethyl)succinamate (ca. 0.2mmol) in DMSO (1ml) was then added dropwise and the mixture stirred overnight at room temperature. The yellow solution was then concentrated (50 /10⁻⁵ mmHg) and the yellow residue partitioned between water and chloroform. The aqueous layer was separated, washed with chloroform (3X) and ethyl acetate, and then concentrated to give an oil (99mg). The crude product was converted to the sodium salt by passage through a column of Amberlite IR 120(Na) to yield 81 mg of material. This material was further purified by gel filtration Sephadex LH20; water) to give the sodium N-(2-sulfoethyl)succinamide terminated (SEQ ID NO: 3) BHAlyslys₂lys₄lys₈lys₁₆ dendrimer (39mg). ¹³C nmr(D₂O):δ 27.0, 32.3, 35.2, 35.3, 35.6, 35.7, 39.5, 43.5, 54.1, 58.5, 131.5, 132.0, 133.3, 145.1, 177.8, 178.0, 178.4, 178.8, 178.9, 179.2, 179.7, 179.8.

Please replace the paragraphs beginning on page 22 at lines 4, with the following rewritten paragraph:


 The corresponding [(SEQ ID NO: 1)] BHAlyslys₂, BHAlyslys₂lys₄ (**BRI2787**) and (SEQ ID NO: 2) BHAlyslys₂lys₄lys₈ (**BRI2788**) terminated with sodium N-(2-sulfoethyl) succinamide groups were similarly prepared. ¹³C nmr (SEQ ID NO: 2) BHAlyslys₂lys₄lys₈ derivative (D₂O):δ 26.9, 32.3, 35.1, 35.3, 35.6, 35.7, 39.5, 43.5, 54.1, 58.5, 131.6, 131.9, 132.2, 132.3, 133.2, 133.3, 145.0, 145.2, 177.2, 177.8, 177.9, 178.0, 178.2, 178.3, 178.6, 178.7, 178.8, 178.9, 179.2, 179.3, 179.7, 179.8.
¹³C nmr (SEQ ID NO: 1) BHAlyslys₂lys₄ derivative (D₂O):δ 26.9, 32.3, 35.1, 35.4, 35.7, 35.8, 39.5, 43.5, 54.1, 58.5, 61.8, 131.7, 132.0, 132.2, 132.3, 133.2, 133.3, 145.0, 145.1, 177.3, 178.0, 178.3, 178.4, 178.7, 178.9, 179.0, 179.3, 179.7, 179.8.
¹³C nmr BHAlyslys₂ derivative (D₂O):δ 26.9, 27.1, 32.2, 32.3, 34.7, 34.8, 35.1, 35.3, 35.6, 35.7, 39.5, 43.4, 54.1, 58.6, 61.8, 131.7, 131.9, 132.2, 132.3, 133.3, 144.9, 145.0, 177.7, 178.4, 178.8, 179.0, 179.3, 180.0.

Please replace paragraph beginning on page 23 at line 19, with the following rewritten paragraph:

(SEQ ID NO: 3) BHAlyslys₂lys₄lys₈lys₁₆ **BRI2792**

Trifluoroacetic acid (4ml) was added to a suspension of (SEQ ID NO: 2) BHAlyslys₂lys₄lys₈DBL₁₆ (0.73g; 0.1mmol) in dry dichloromethane (4ml) under nitrogen. A vigorous evolution of gas was observed for a short time and the resulting solution was stirred at room temperature for two hours and then concentrated. The residual syrup was dissolved in water (5ml), the solution passed through a column of Amberlite IRA-401(OH) and the filtrate concentrated to give (SEQ ID NO: 3) BHAlyslys₂lys₄lys₈lys₁₆ as a viscous oil (0.49g). The oil was redissolved in water (5ml) and N,N-dimethyl-N-allylamine buffer (pH 9.5; 3ml) added. Solid sodium 4-sulfophenylisothiocyanate monohydrate (1.30g; 5.1mmol) was then added and the resulting solution heated under nitrogen at 53 °C for two hours and then cooled. The solution was concentrated and the brownish solid residue purified by gel filtration (Sephadex LH20; water). The pure fractions were combined, passed through a column of Amberlite IR 120(Na) and freeze dried to give the sodium 4-sulfophenylthiourea terminated (SEQ ID NO: 3) BHAlyslys₂lys₄lys₈lys₁₆ dendrimer as a fluffy white solid (374mg). ¹H nmr (D2O): δ 1.40; 1.72; 3.08; 3.42; 4.24; 4.60; 7.30; 7.40 (d, J = 9Hz); 7.78 (d, J = 9Hz). ¹³C nmr (D2O): δ 27.3; 32.5; 35.9; 43.7; 48.9; 58.6; 63.3; 128.8; 131.0; 143.7; 144.7; 145.1; 177.7; 178.1; 183.8; 185.2.

Please replace the paragraph beginning on page 24 at line 8, with the following rewritten paragraph:

The corresponding (SEQ ID NO: 2) BHAlyslys₂lys₄lys₈, (SEQ ID NO: 4) BHAlyslys₂lys₄lys₈lys₁₆lys₃₂ (**BRI2992**), and (SEQ ID NO: 5) BHAlyslys₂lys₄lys₈lys₁₆lys₃₂lys₆₄ (**BRI2993**) dendrimers terminated with 16, 64, and 128 sodium 4-sulfophenylthiourea groups respectively were similarly prepared.

Please replace the paragraph beginning on page ~~23~~²⁴ at line 13, with the following rewritten paragraph:

C5 BHAlyslys2lys4lys8lys16lys32lys64 (**BRI2993**) dendrimers terminated with 16, 64, and 128 sodium 4-sulfophenylthiourea groups respectively were similarly prepared.

Please replace the paragraph beginning on page 25 at line 13, with the following rewritten paragraph:

(SEQ ID NO: 3) BHAlyslys2lys4lys8lys16 **BRI2999**

Trifluoroacetic acid (2ml) was added to a suspension of (SEQ ID NO: 2)

BHAlyslys2lys4lys8 DBL16 (0.73g; 0.1mmol) in dry dichloromethane (2ml) under nitrogen.

C6 A vigorous evolution of gas was observed for a short time and the resulting solution was stirred at room temperature for two hours and then concentrated. The residual syrup was dissolved in water (5ml), the solution passed through a column of Amberlite IRA-401(OH) and the filtrate concentrated to give (SEQ ID NO: 3) BHAlyslys2lys4lys8lys16 as a viscous oil (0.49g). The oil was redissolved in water (5ml) and N,N-dimethyl-N-allylamine buffer (pH 9.5; 3ml) added. Solid sodium 3,6-sulfophenylisothiocyanate (234mg; 0.60mmol) was then added and the resulting solution heated under nitrogen at 53 for two hours and then cooled. The solution was concentrated and the brownish solid residue purified by gel filtration (Sephadex LH20; water). The pure fractions were combined, passed through a column of Amberlite IR 120(Na) and freeze dried to give (SEQ ID NO: 3) BHAlyslys2lys4lys8lys16 terminated with 32 sodium 3,6-disulfonaphthylthiourea groups as a fluffly off-white solid (119mg). ¹H nmr (D2O):δ 1.0-2.0; 3.18; 3.43; 4.31; 7.22; 7.80; 7.89; 8.25. ¹³C nmr (D2O):δ 27.2; 32.4; 35.3; 43.7; 49.0; 58.5; 63.6; 128.4; 129.1; 131.4; 136.1; 136.6; 138.6; 139.0; 145.6; 178.4; 184.8; 186.7.

Please replace the paragraph beginning on page 27 at line 18, with the following rewritten paragraph:

C7 The corresponding sodium 3,6,8-trisulfonaphthylthiourea terminated dendrimer (SEQ ID NO: 3) BHAlyslys2lys4lys8lys16 **BRI 7011** was prepared similarly.

Please replace the paragraph beginning on page 30 at line 9, with the following rewritten paragraph:

CS (SEQ ID NO: 3) BHAlyslys2lys4lys8lys16 **BRI 2922**

Trifluoroacetic acid (4ml) was added to a suspension of (SEQ ID NO: 2) BHAlyslys2lys4lys8 DBL16 (220mg; 30 μ mol) in dry dichloromethane (2ml) and the resulting solution stirred at room temperature under nitrogen for two hours and then concentrated. The residue was dissolved in dry DMSO (5ml) and the pH adjusted to 8.5 with triethylamine. Solid 4-nitrophenyl N,N,N-trimethylglycinate chloride (0.50g; 1.8mmol) was then added and the mixture stirred overnight at room temperature. The cloudy solution was then concentrated (50 /10⁻⁵ mmHg) and the residue partitioned between water and dichloromethane. The aqueous layer was separated, washed with dichloromethane (3X) and ethyl acetate, and then concentrated to give an oil (1.128g). The crude product was purified by gel filtration (Sephadex LH20; water) to give the N,N,N-trimethylglycinamide terminated (SEQ ID NO: 3) BHAlyslys2lys4lys8lys16 dendrimer (116mg). ¹³C nmr (D₂O): δ 25.5, 30.5, 30.8, 33.4, 42.1, 56.5, 57.1, 67.5, 68.1, 166.7, 167.0, 167.1, 176.0, 176.2.

Please replace the paragraph beginning on page 39 at line 31 with the following rewritten paragraph:

CG (SEQ ID NO: 3) BHAlyslys2lys4lys8lys16 [8-octanamido)- 5-acetamido-3,5-dideoxy-2-thio D-glycero- α -D-galacto-2-nonulopyranosidoic acid]₃₂ **BRI 6169**

Please replace the paragraph beginning on page 40 at line 3 with the following rewritten paragraph:

CG10 A solution of (SEQ ID NO: 3) BHA lyslys2lys4lys8lys16 (t-Boc)₃₂ (20.3mg.) in a mixture of trifluoroacetic acid (2ml.) and dichloromethane (2ml.) was stirred at 20 C for 2 hours

C10
only

then solvent was removed under vacuum. The residue was dissolved in dry dimethyl sulphoxide (1ml.) and di-isopropylethylamine (25mg.) and methyl [(8-octanoic acid N-hydroxysuccinimide ester) 5-acetamido-4,7,8,9-tetra-O-acetyl- α -D-glycero- α -D-galacto-2-nonulopyranosid]onate (78mg.) were added. The mixture was stirred under argon at 20 C for 60 hours then solvent was removed under vacuum. The residue was dissolved in a freshly prepared 0.1M solution of sodium methoxide in methanol (2.5ml.) and the mixture stirred for 3 hours under argon at 20 C. The solvent was evaporated and the residue dissolved in water (1ml.) and stirred for 17 hours. This solution was subjected to size exclusion chromatography on Sephadex LH20 eluting with water. After lyophilisation, the product, (SEQ ID NO: 3) BHA lyslys₂lys₄lys₈lys₁₆ [(8-octanamido)-5- acetamido-3,5-dideoxy-2-thio-D-glycero- α - D-galacto-2-nonulopyranosidoic acid]₃₂ was obtained as a white powder 44mg. 86%.

Please replace the paragraph on page 13, between lines 21-24 with the following rewritten paragraphs:

C11

Figure 1 Effect of 10e-4M BR12923 on the cell toxicity caused by 10e-5M HIV Vpr peptide fraction P3 (not corrected).

Figure 2 Effect of 10e-4M BR12923 on the cell toxicity caused by 10e-5M HIV Vpr peptide fraction P3 (corrected).

Figure 3 Effect of 10e-5M BR12923 on the cell toxicity caused by 2x10e-5M HIV Vpr peptide fraction P3 (not corrected).

Figure 4 Effect of 10e-5M & 10e-7M BR12923 on the cell toxicity caused by 2x10e-5M HIV Vpr peptide fraction P3 (not corrected).

In the Abstract:

Please add the Abstract which is appended to the Amendment.

In the Claims:

In accordance with 37 CFR § 1.121, please substitute for original claims 1, 2 and 7-12, the following rewritten versions of the same claims, as amended. The

changes are shown explicitly in the attached "Marked Up Version Showing Changes Made."

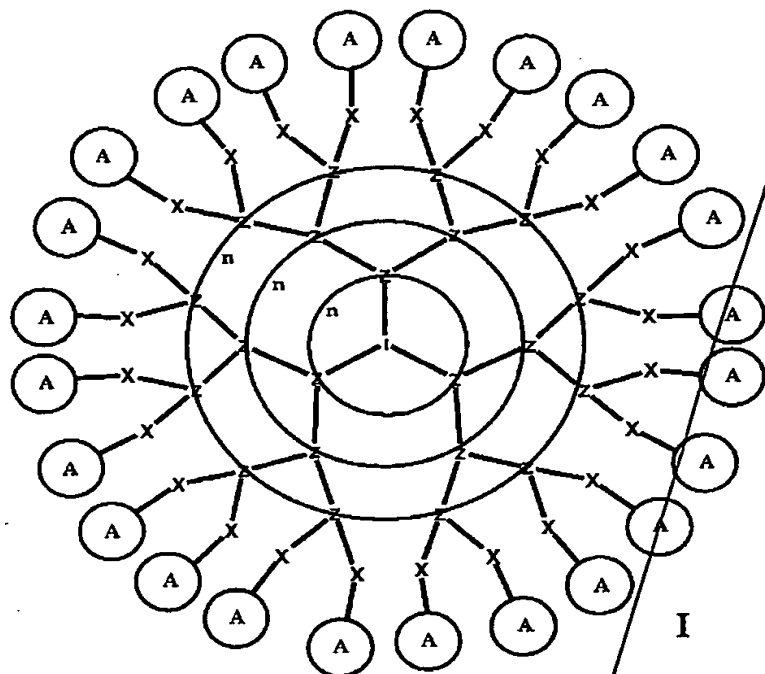
Please cancel claim 13 without prejudice or disclaimer.

Sub
D
12

1. (Amended) A method of inhibiting the activity of a toxic material or substance in a human or non-human animal patient, which comprises administration of the patient of an effective amount of a dendrimer having a plurality of terminal groups wherein at least one of said terminal groups has an anionic- or cationic-containing moiety bonded or linked thereto.

2. (Amended) A method according to claim 1, wherein said dendrimer comprises a polyvalent core covalently bonded to at least two dendritic branches, and extends through at least two generations.

7. (Amended) A method according to claim 2 wherein said is a polyionic dendrimer of the general formula I:



wherein:

I is an initiator core;

Z is an interior branching unit;

n is an integer which represents the number of generations of the dendrimer; and

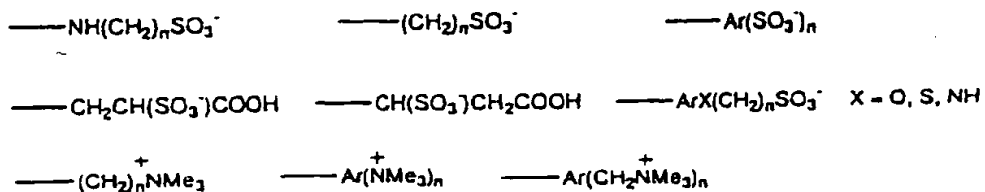
A is an anionic- or cationic containing moiety which may be linked to interior branching unit Z through an optional linking group X.

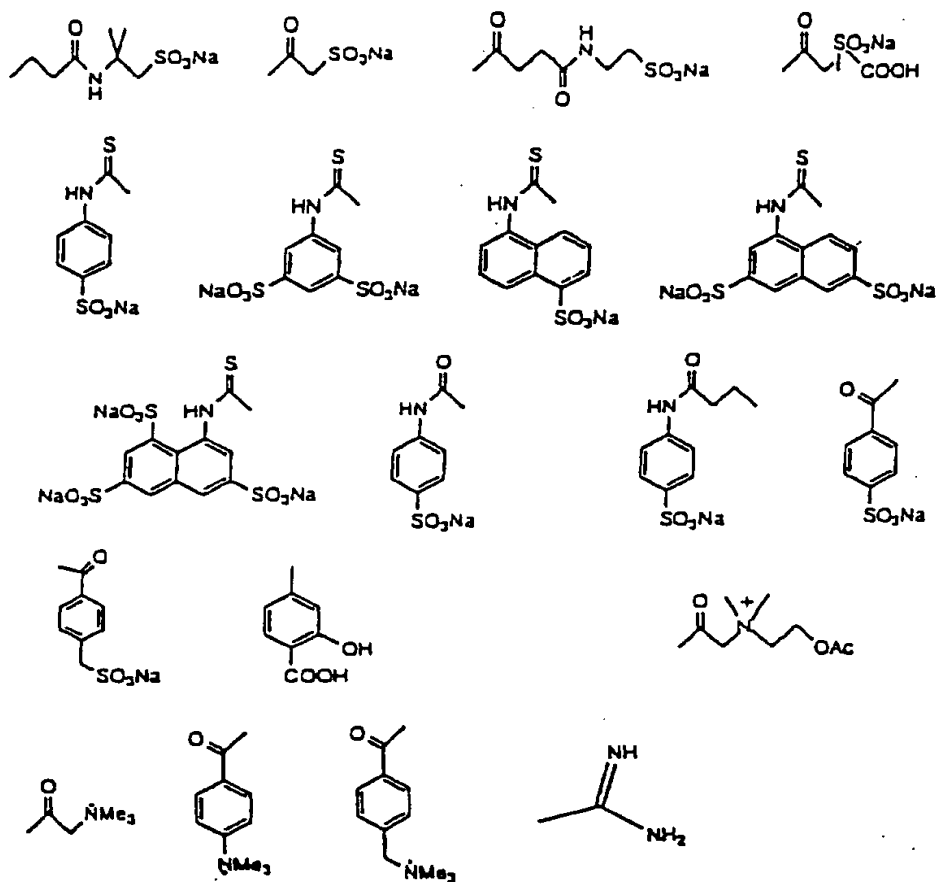
8. (Twice Amended) A method according to claim 1, wherein in said dendrimer said anionic- or cationic-containing moiety or moieties are bonded to amine, sulfhydryl, hydroxy or other reactive terminal groups of the dendrimer by amide or thiourea linkages.

9. (Twice Amended) A method according to claim 1, wherein in said dendrimer said anionic- or cationic-containing moieties are selected from the group consisting of sulfonic acid-containing moieties, carboxylic acid-containing moieties,

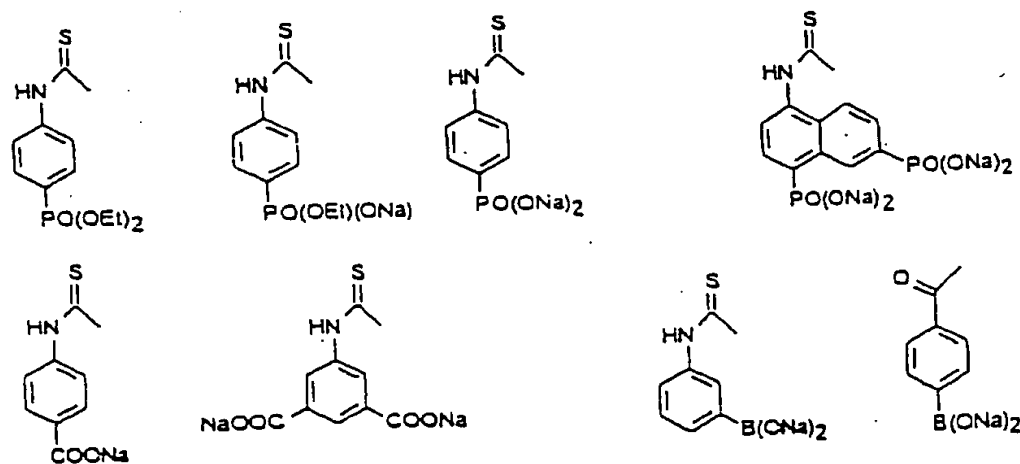
neuraminic and sialic acid-containing moieties, modified neuraminic and sialic acid-containing moieties, boronic acid-containing moieties, phosphoric and phosphonic acid-containing moieties, esterified phosphoric and phosphonic acid-containing moieties, primary, secondary, tertiary or quaternary amino-containing moieties, pyridinium-containing moieties, guanidinium-containing moieties, amidinium-containing moieties, phenol-containing moieties, heterocycles possessing acidic or basic hydrogens, and zwitterionic-containing moieties.

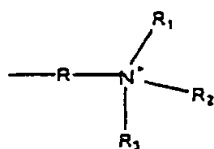
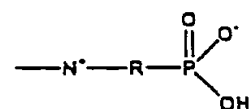
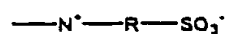
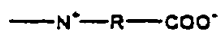
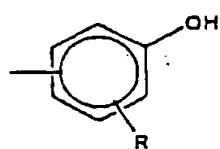
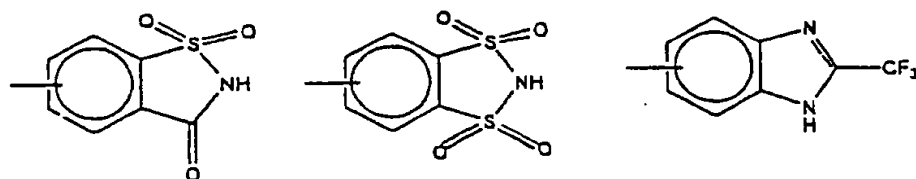
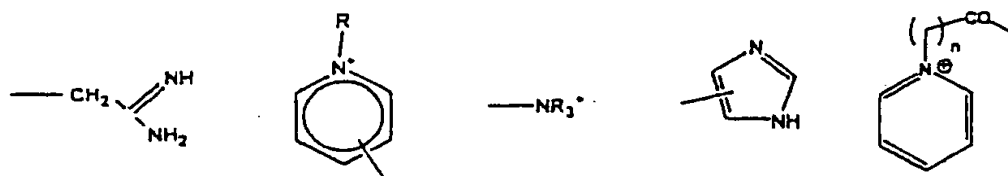
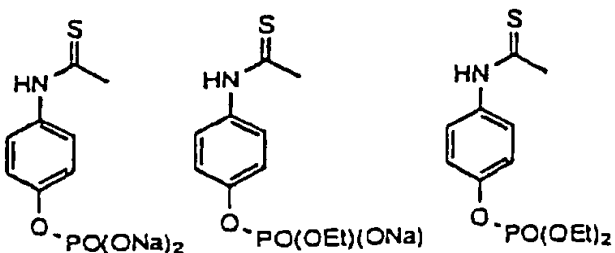
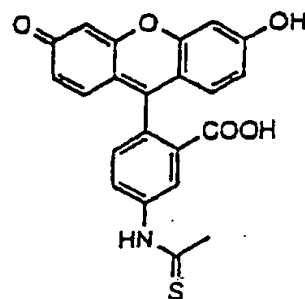
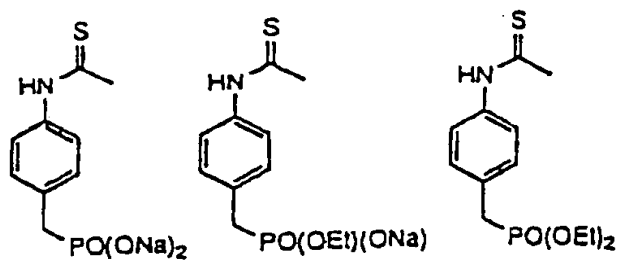
10. (Twice Amended) A method according to claim 1, wherein in said dendrimer the moiety or moieties which are bonded to amino or other reactive terminal groups of the dendrimer are selected from the following groups, in which n is zero or a positive integer:



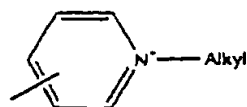


—ArXP(=O)(OR)_2 $\text{X=O, CH}_2, \text{CHF, CF}_2$ $\text{R=alkyl, aryl, H, Na.}$
 $\text{—ArXP(=O)(OR')}(NR^2R^3)$ $\text{X=O, CH}_2, \text{CHF, CF}_2$ $\text{R'}=\text{alkyl, aryl, H, Na}$ $\text{R}^2, \text{R}^3=\text{alkyl, aryl}$
 $\text{—Ar[P(=O)(OR)}_2\text{]}_n$ $\text{R=alkyl, aryl, H, Na}$ $n=1-3$
 $\text{—Ar[B(OH)}_2\text{]}_n$ $n=1-3$ —Ar[COOH]_n $n=1-3$






R = alkyl or arylalkyl; R₁, R₂, R₃ (which may be same or different) = alkyl or arylalkyl



11. (Twice Amended) A method according to claim 1, wherein said dendrimer is selected from the group consisting of:

- 
- i. alkylsulfonic acid terminated dendrimers;
 - ii. sulfoacetamide terminated dendrimers;
 - iii. sulfosuccinamic acid terminated dendrimers;
 - iv. N-(2-sulfoethyl) succinamide terminated dendrimers;
 - v. 4-sulfophenylthiourea terminated dendrimers;
 - vi. 3,6-di-sulfonaphthylthiourea terminated dendrimers;
 - vii. 4-sulfonaphthylthiourea terminated dendrimers;
 - viii. 3,5-di-sulfophenylthiourea terminated dendrimers;
 - ix. 3,6,8-tri-sulfonaphthylthiourea terminated dendrimers;
 - x. 4-(sulfomethyl) benzamide terminated dendrimers;
 - xi. 4-sulfobenzamide terminated dendrimers;
 - xii. N-(4-sulfophenyl) propanamide terminated dendrimers;
 - xiii. 4-sulfophenylurea terminated dendrimers;
 - xiv. N,N,N-tri-methylglycinamide terminated dendrimers;
 - xv. 4-trimethylammonium benzamide terminated dendrimers;
 - xvi. 4-(trimethylammoniummethyl)benzamide terminated dendrimers;
 - xvii. N-(2-acetoxyethyl)-N,N-(dimethylammonium)methyl-carboxamide terminated dendrimers;
 - xviii. guanidino terminated dendrimers;
 - xix. 4-([1,4,8,11-tetraazacyclotetradecane]methyl)benzamide terminated dendrimers;
 - xx. 4-carboxy-3-hydroxy-benzylamine terminated dendrimers;
 - xxi. 4-carboxyphenylamide terminated dendrimers;
 - xxii. 3,5-dicarboxyphenylamide terminated dendrimers;
 - xxiii. 4-phosphonooxyphenylthiourea terminated dendrimers;
 - xxiv. 4-(phosphonomethyl)phenylthiourea terminated dendrimers;
 - xxv. ethyl-4-(phosphonomethyl)phenylthiourea terminated dendrimers;
 - xxvi. (8-octanamido)-5-acetamido-3,5-dideoxy-2-thio-D-glycero- β -D-galacto-2-nonulopyranosidoic acid terminated dendrimers;

- xxvii. (11-undecanamido)-5-acetamido-3,5-dideoxy-2-thio-D-glycero- β -D-galacto-2-nonulopyranosidoic acid terminated dendrimers;
- xxviii. (acetamido)-5-acetamido-3,5-dideoxy-2-thio-D-glycero- β -D-galacto-2-nonulopyranosidoic acid terminated dendrimers;
- xxix. (4-butanamido)-5-acetamido-3,5-dideoxy-2-thio-D-glycero- β -D-galacto-2-nonulopyranosidoic acid terminated dendrimers;
- xxx. (4-methylbenzamido)-5-acetamido-3,5-dideoxy-2-thio-D-glycero- β -D-galacto-2-nonulopyranosidoic acid terminated dendrimers;
- xxxi. (8-octanamido)-4-azido-5-acetamido-3,4,5-trideoxy-2-thio-D-glycero- β -D-galacto-2-nonulopyranosidoic acid terminated dendrimers;
- xxxii. (8-octanamido)-4-amino-5-acetamido-3,4,5-trideoxy-2-thio-D-glycero- β -D-galacto-2-nonulopyranosidoic acid terminated dendrimers;
- xxxiii. 4-benzamidoboronic acid terminated dendrimers;
- xxxiv. 3,5-dicarboxyphenylthiourea terminated dendrimers;
- xxxv. 4-phosphonooxyphenylthiourea terminated dendrimers;
- xxxvi. 4-phosphonophenylthiourea terminated dendrimers;
- xxxvii. 4,6-diphosphononaphthylthiourea terminated dendrimers;
- xxxviii. fluoresceinthiourea terminated dendrimers;
- xxxix. (phenyl-3-boronic acid)-thiourea terminated dendrimers;
- xl. pyridinium dodecylcarboxamide terminated dendrimers; and
- saccharin terminated dendrimers.

12. (Twice Amended) A method according to claim 1, wherein said method comprises inhibition of toxins and toxic peptides of biological origin or toxins and toxic peptides released during bacterial, protozoal, fungal or viral infection.